IN THE NAME OF GOD

WEBINAR

LUTEAL PHASE *Support*

NOURISHING THE WINDOW OF IMPLANTATION



Supervisor: Dr. Firoozeh Ghafari

Presented by :Dr. Nastaran Abolghasem

LUTEAL PHASE *Support*



NOURISHING TODAY,
FOR A SUCCESSFUL TOMORROW

PROGESTERONE
The key hormone for endometrial receptivity

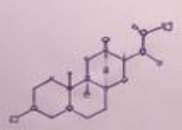
OPTIMAL ENDOMETRIUM
Promotes a receptive and nurturing lining

IMMUNE BALANCE
Supports tolerance for implantation

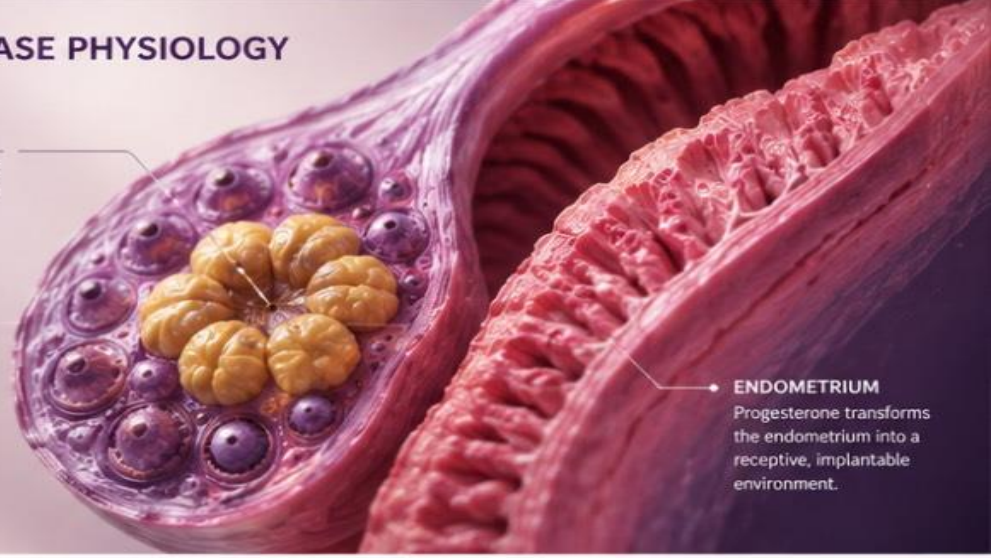
EARLY PREGNANCY
Improves chances of implantation and continuation

LUTEAL PHASE PHYSIOLOGY

CORPUS LUTEUM
Produces progesterone to prepare and maintain the endometrium.



PROGESTERONE
The central hormone for luteal phase and implantation.



ENDOMETRIUM
Progesterone transforms the endometrium into a receptive, implantable environment.

PROGESTERONE ⟶ ENDOMETRIAL RECEPTIVITY ⟶ IMPLANTATION



PROGESTERONE
Secreted by corpus luteum (and/or supplemented) to support the luteal phase.

ENDOMETRIAL TRANSFORMATION
Increases thickness, vascularity, and glandular secretion.

IMMUNE MODULATION
Promotes immune tolerance and reduces inflammation.

IMPLANTATION
Optimal environment for embryo implantation and early pregnancy.

PREGNANCY MAINTENANCE
Supports early placentation and pregnancy continuation.

LUTEAL PHASE SUPPORT OPTIONS

VAGINAL
- Progesterone gel
- Progesterone capsule
- Progesterone tablet

High endometrial concentration

ORAL
- Micronized progesterone
- Dydrogesterone

Easy to use, good compliance



GOAL
Adequate progesterone exposure for implantation and early pregnancy maintenance

INTRAMUSCULAR
- Progesterone in oil

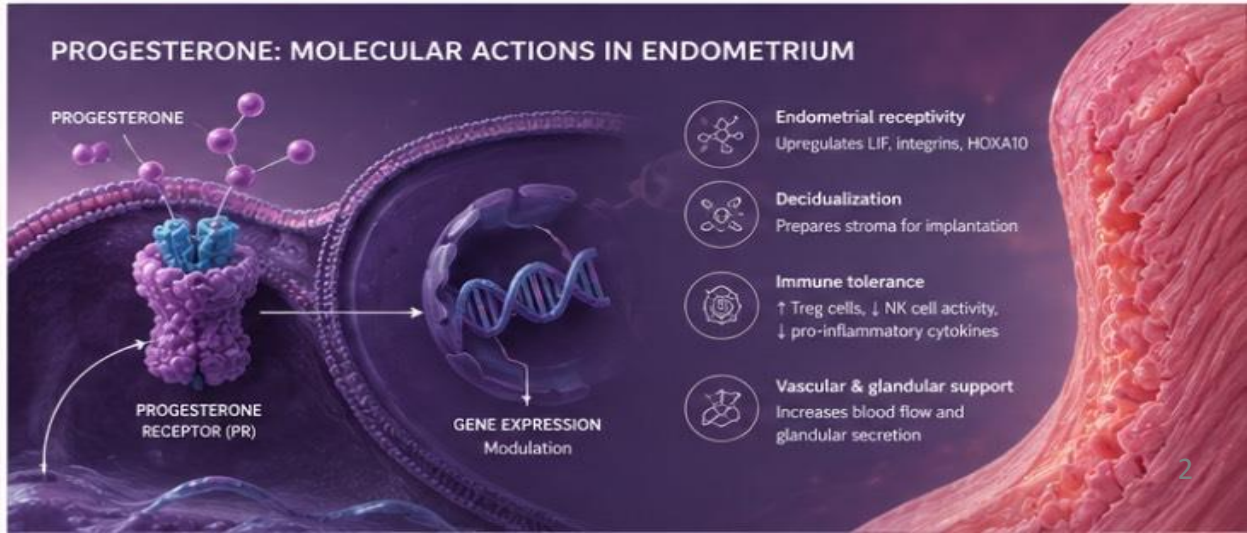
Effective systemic levels

SUBCUTANEOUS
- Progesterone in oil

Alternative to IM, better tolerability

✓ Individualized approach ✓ Based on cycle type, patient factors ✓ Evidence-based benefit

PROGESTERONE: MOLECULAR ACTIONS IN ENDOMETRIUM



Endometrial receptivity
Upregulates LIF, integrins, HOXA10

Decidualization
Prepares stroma for implantation

Immune tolerance
↑ Treg cells, ↓ NK cell activity, ↓ pro-inflammatory cytokines

Vascular & glandular support
Increases blood flow and glandular secretion

Physiology of the Luteal Phase

The luteal phase begins after ovulation

functional activity of the corpus luteum (CL).

Following the LH surge and follicular rupture, granulosa and theca cells undergo luteinization, transforming the ruptured follicle into a highly steroidogenic corpus luteum.

Corpus luteum produces predominantly progesterone, together with estradiol and other steroid hormones.

LH stimulation of the LH/hCG receptor on luteal cells promotes steroidogenesis and maintains corpus luteum function.

In a natural menstrual cycle, pulsatile LH secretion provides the trophic stimulus required for continued luteal activity.

The major physiological sequence is:

LH surge → Ovulation → Luteinization → Corpus luteum formation → Progesterone + Estradiol secretion

Progesterone secretion rises rapidly after ovulation and reaches its peak approximately 5–8 days after ovulation, corresponding to the period when the endometrium becomes maximally receptive.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

Progesterone and endometrial transformation

Progesterone converts the estrogen-primed proliferative endometrium into a secretory and implantation-receptive endometrium.

Its major effects include:

Transformation of endometrial glands and stromal cells

Regulation of endometrial gene expression **Development of a receptive endometrial phenotype**

Modulation of endometrial receptivity and implantation **Regulation of uterine contractility**

Modulation of local immune and inflammatory pathways* Preparation of the endometrium for embryo implantation and early pregnancy

Importantly, implantation depends not only on adequate progesterone concentrations but also on the timing and duration of progesterone exposure relative to embryo development.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

The Window of Implantation

Progesterone exposure initiates a sequence of molecular and cellular changes that creates the window of implantation (WOI).

During this period, the endometrium becomes receptive to the developing embryo through coordinated changes involving:

Progesterone signaling → Endometrial differentiation → Molecular remodeling → Receptive endometrium → Embryo implantation

Therefore, luteal phase function is fundamentally a question of both hormonal adequacy and endocrine–embryonic synchrony.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

What happens if pregnancy does not occur?

In the absence of implantation, there is no sustained embryonic hCG signal. The corpus luteum subsequently undergoes luteolysis, resulting in a progressive decline in progesterone and estradiol.

↓ Progesterone + ↓ Estradiol→ Endometrial breakdown→ Menstruation

Loss of steroid negative feedback also contributes to the subsequent rise in FSH and recruitment of follicles for the next menstrual cycle.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

What changes when implantation occurs?

Following implantation, trophoblast-derived hCG rescues the corpus luteum.

Because hCG acts through the same LH/hCG receptor, it maintains luteal steroidogenesis and prevents corpus luteum regression.

Embryo implantation→Trophoblastic hCG secretion → LH/hCG receptor stimulation → Corpus luteum rescue → Continued progesterone production → Maintenance of the endometrium

During early pregnancy, the corpus luteum remains an important source of progesterone. With advancing gestation, steroidogenic activity progressively shifts toward the placenta—the luteo-placental shift, classically occurring around 8–10 weeks of gestation.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

Why is this important in ART?

The luteal phase following controlled ovarian stimulation is not necessarily physiologically equivalent to a natural luteal phase.

Multiple corpora lutea, supraphysiologic steroid concentrations, altered LH dynamics, and the type of ovulation trigger can affect luteal function.

The problem can be particularly pronounced after a GnRH agonist trigger, where rapid luteolysis and profound reduction in LH activity may occur.

Luteal phase support aims to compensate for inadequate endogenous luteal steroid production and to maintain an endometrial environment compatible with implantation and early pregnancy.

ESHRE Guideline Group. Hum Reprod. 2026;41(4):498–514.

ESHRE Guideline Group. Hum Reprod Open. 2020;2020(2):hoaa009.

Learning objectives

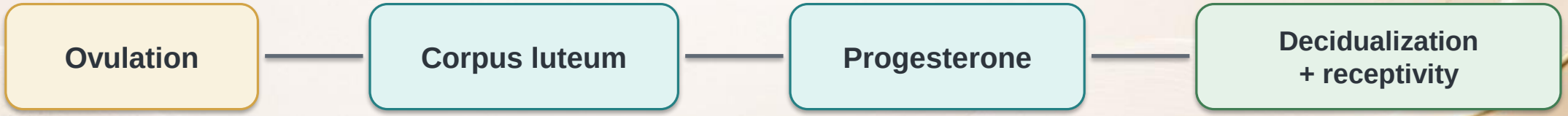
- Understand why luteal phase support (LPS) is needed after ovarian stimulation and in different FET protocols.
- Distinguish fresh transfer, true natural-cycle FET, modified natural-cycle FET, and artificial/HRT FET.
- Compare progesterone routes, adjuvants, timing, and serum progesterone considerations.
- Translate the evidence into practical decisions for fresh ET and FET.
- Recognize where evidence is strong—and where personalization remains investigational.

Core question

Is the “right” luteal support simply enough progesterone—or the right progesterone exposure at the right time?

Why luteal support matters

- The corpus luteum (CL) is a temporary endocrine structure formed after ovulation.
- It secretes progesterone, estrogen, relaxin, and vasoactive/angiogenic mediators.
- Progesterone drives endometrial decidualization and establishes endometrial receptivity.
- Implantation occurs during a narrow “window of implantation” (WOI).
- LPS supplies luteal hormones when endogenous support is insufficient or absent.



What is luteal phase support?

- LPS = administration of hormonal products of the corpus luteum, either alongside an active CL or when a CL is absent.
- It may be used after controlled ovarian stimulation followed by oocyte retrieval, after ovulation induction/IUI, or for preparation of FET.
- Progesterone is the principal component supported by the review.
- The rationale differs fundamentally between cycles with a functioning CL and cycles without a CL.

With a corpus luteum

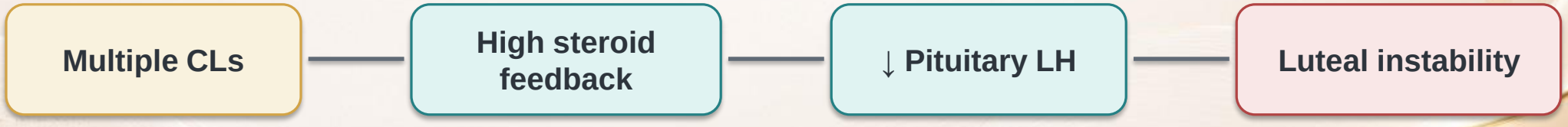
Support endogenous luteal function or supplement progesterone.

Without a corpus luteum

Exogenous estrogen + progesterone must create and maintain the hormonal environment.

Why IVF stimulation can create luteal dysfunction

- Controlled ovarian stimulation creates multiple corpora lutea after oocyte retrieval.
- High steroid production can exert strong negative feedback on pituitary LH secretion.
- Reduced LH stimulation may contribute to premature luteolysis and a fall in endogenous progesterone.
- Progesterone withdrawal can lead to endometrial shedding unless luteal support is provided.
- This is one reason LPS became a standard component of stimulated IVF cycles.



Fresh embryo transfer: what is different?

- Endometrial proliferation and decidualization occur as by products of ovarian stimulation.
- At the same time, the stimulation/retrieval process alters luteal physiology.
- Three broad strategies can support the luteal phase by preventing the premature drop in the LH stimulation of the CL to secrete progesterone
    - Supplement progesterone.
    - Stimulate the CL with hCG or GnRH agonist.
    - Combine approaches.
- progesterone as the core LPS strategy.

Progesterone LPS in fresh ET: efficacy

8 RCTs • 875 women

Progesterone vs placebo/no treatment: ongoing pregnancy OR 1.77 (95% CI 1.09–2.86).

When beyond the first pregnancy test and until 12 weeks of pregnancy

Effect appeared stronger: ongoing pregnancy OR 2.17 (95% CI 1.37–3.43).

- The benefit is statistically significant but described as modest in the overall analysis.
- The review therefore supports progesterone LPS after fresh embryo transfer.
- Duration of support may influence the magnitude of benefit in the analyzed trials.

van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. (2015)

Should we add hCG to progesterone?

16 RCTs, 2162 women

Strategy	Pregnancy benefit	OHSS signal	Clinical interpretation
Progesterone alone	improve ongoing pregnancy rate	Lower	Preferred core LPS
Progesterone + hCG	No demonstrated advantage	↑ OHSS	Not supported by review

Bottom line

Adding hCG did not improve outcomes over progesterone alone, while OHSS was significantly more frequent .

van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. (2015

Should we add estradiol?

- Nine RCTs (2577 women) evaluated estrogen added to progesterone LPS.
- Estrogen was administered through several routes.
- The meta-analysis did not demonstrate improved ongoing pregnancy rate.
- The lack of benefit was consistent regardless of the estrogen route examined.
- Therefore, routine estradiol addition is not supported by this review.

Clinical pearl

More hormones ≠ better luteal support. The key is physiologic adequacy, not simply adding agents.

van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. (2015

GnRH agonist as an adjuvant in fresh ET

7 RCTs, 1708 women

Evidence signal

Adding GnRH agonist to progesterone improved ongoing pregnancy vs progesterone alone

- The review reports benefit with single-dose or repeated GnRH agonist administration.
- No increased OHSS risk was demonstrated in the cited meta-analysis.
- Mechanistic interpretation: additional luteotrophic support may help stabilize CL function.
- However, protocol details matter—especially the relationship to trigger strategy.

van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. (2015

GnRH Agonist as an Adjunct to Progesterone

Does an additional GnRHa improve luteal function?

BIOLOGICAL RATIONALE

After an hCG trigger, a GnRHa bolus can induce an additional pituitary LH/FSH release.

Theoretical aim: reinforce corpus luteum function and progesterone production.

But biological plausibility ≠ proven clinical benefit.

CURRENT EVIDENCE

- Progesterone remains the established LPS after IVF/ICSI.
- GnRHa + progesterone after hCG trigger has not shown consistent improvement in reproductive outcomes.
- Repeated GnRHa administration is not established as routine LPS.
- Evidence remains heterogeneous and insufficient to replace standard progesterone support.

ESHRE 2025/2026 — PRACTICE POINT

A GnRH agonist bolus in addition to progesterone in hCG-triggered cycles is probably NOT recommended.

Repeated GnRH agonist injections, alone or combined with progesterone, are also probably NOT recommended.

CLINICAL TAKE-HOME

GnRHa is not a routine “booster” of progesterone-based LPS after an hCG trigger.

Key reference: ESHRE Guideline on ovarian stimulation for IVF/ICSI — update 2025, Human Reproduction (2026).

GnRH agonist trigger: a special fresh-ET scenario

- GnRH agonist trigger is commonly used in patients at increased OHSS risk or in freeze-all strategies.
- If a fresh transfer follows an agonist trigger, luteal support becomes challenging.
- The central problem is balancing rapid luteolysis against the desire to minimize OHSS.
- Adding hCG can restore luteotrophic stimulation—but may reintroduce OHSS risk.

Key safety principle

Lone GnRH-agonist trigger without hCG luteal rescue is the strategy associated with elimination of OHSS in the cited meta-analysis.

Elgindy EA et al. Towards an optimal luteal support modality in agonist triggered cycles: a randomized clinical trial. Hum Reprod. (2018)
. Safrai M, et al. Dydrogesterone supplementation in addition to routine micronized progesterone administration for luteal support in cycles triggered with lone GnRH agonist results in an acceptable pregnancy rate and avoids the need to freeze embryos. Minerva Obstet Gynecol. (2021).
Ioannidou PG, et al. How frequent is severe ovarian hyperstimulation syndrome after GnRH agonist triggering in high-risk women? a systematic review and meta-analysis. Reprod Biomed Online. (2021)

GnRH Agonist Trigger + Fresh Embryo Transfer

The issue is inadequate sustained luteotrophic support — not absence of a corpus luteum

GnRHa trigger
LH/FSH surge

Ovulation
Corpus luteum forms

Rapid LH decline
Short-lived luteotrophic support

↓ luteal P4
Luteal phase insufficiency

KEY PHYSIOLOGY

GnRHa trigger DOES NOT abolish corpus luteum formation.

The LH surge is brief, followed by rapid loss of endogenous LH activity.

Multiple corpora lutea therefore receive less sustained luteotrophic stimulation → lower/shorter progesterone exposure.

FRESH ET: ESHRE 2025/2026

GnRH agonist trigger is NOT recommended in the general IVF/ICSI population undergoing fresh embryo transfer, regardless of the type of luteal support.

Major safety role remains in patients at high risk of OHSS, particularly when a freeze-all strategy is used.

PRACTICAL MESSAGE

GnRHa trigger + Fresh ET → luteal support must address inadequate endogenous LH activity. hCG can rescue luteal function, but increases OHSS concern.

Key references: ESHRE Guideline on ovarian stimulation for IVF/ICSI — update 2025, Human Reproduction (2026); recent randomized fresh-ET studies of hCG luteal rescue.

Route of progesterone in fresh ET

Comparison	Finding in review
IM vs oral	No statistically significant difference
IM vs vaginal/rectal	No statistically significant difference
Low vs high vaginal dose	No significant difference
Micronized vs synthetic	No clear superiority
Vaginal ring / gel	No clear superiority
IM + vaginal vs single route	Retrospective studies: similar outcomes

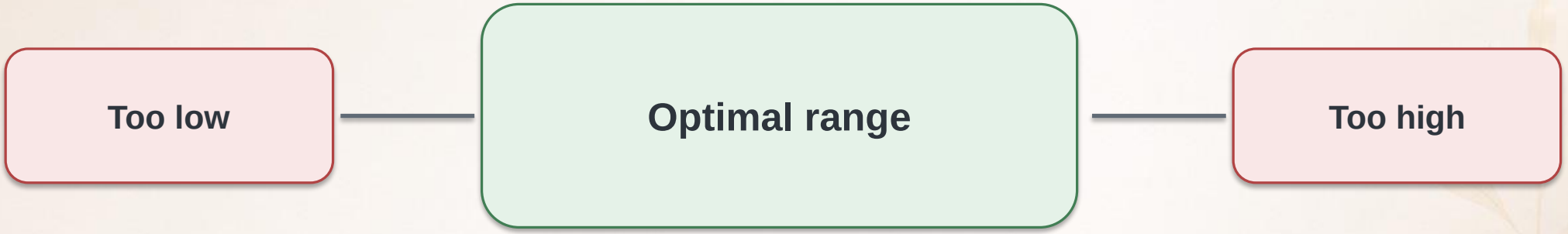
Take-home

No single progesterone route was clearly superior in fresh ET across the cited evidence.

Gari S, Al-Jaroudi D. Adding weekly intramuscular progesterone to a twice daily vaginal progesterone capsule for luteal phase support in IVF/ICSI cycles results in similar live birth rates. (2021).
. Nho EJ, Hong YH, Park JH, Kim SK, Lee JR, Jee BC, et al. Efficacy of dual progesterone administration (intramuscular and vaginal) for luteal support in fresh day 3 or day 4 embryo transfer cycles. . (2020)
van der Linden M, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. (2015

Serum progesterone: the “too low / too high” concept

5 studies comparing ongoing pregnancy rate (OPR) or live birth rate (LBR) in patients receiving a low or a high dose of micronized vaginal progesterone (MVP), found no difference in outcome



Early luteal phase

60–100 nmol/L associated with highest pregnancy/live birth rates.

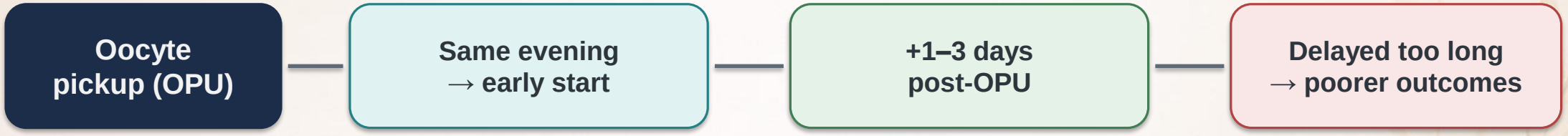
Mid-luteal phase

150–250 nmol/L associated with highest pregnancy/live birth rates.

Labarta E, et al. Individualized luteal phase support normalizes live birth rate in women with low progesterone levels on the day of embryo transfer in artificial endometrial preparation cycles. (2022)

Thomsen LH, et al. The impact of luteal serum progesterone levels on live birth ratesa prospective study of 602 IVF/ICSI cycles. (2018)

Timing LPS in fresh ET



Evidence examples(5 RCT)

12 h before OPU vs 24 h after OPU: 12.9% vs 24.6% in the cited study.(Sohn et al.1999)
Day 3 vs day 6 after OPU: 61.0% vs 44.8%.(Williams et al.2001)

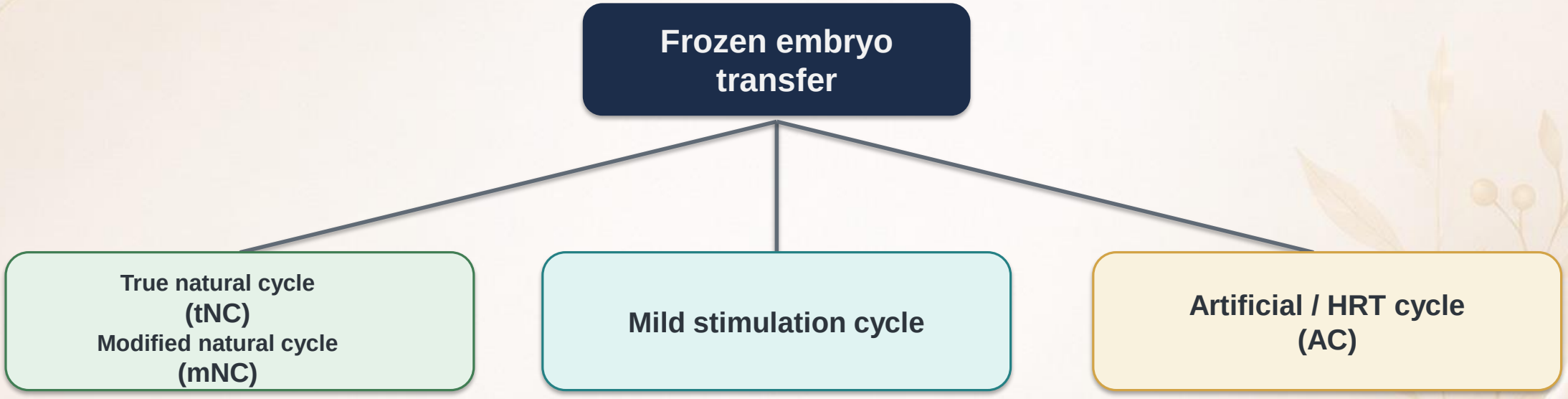
Connell MT, et al. Timing luteal support in assisted reproductive technology: a systematic review. Fertil Steril. (2015) 103:939–46. doi: 10.1016/j.fertnstert.2014.
Sohn SH, et al. Administration of progesterone before oocyte retrieval negatively affects the implantation rate. Fertil Steril. (1999)
Williams SC, et al. Delaying the initiation of progesterone supplementation results in decreased pregnancy rates after in vitro fertilization: a randomized, prospective study. Fertil Steril. (2001)
Kol S. Time, time, time: see what governs the luteal phase endocrinology. Gynecol Endocrinol. (2021)

Fresh ET: practical evidence summary

Question	Evidence summarized in review	Practical message
Progesterone vs none	Benefit in ongoing pregnancy	Use progesterone LPS
Add hCG?	No added benefit; more OHSS	Avoid routine hCG add-on
Add estradiol?	No ongoing pregnancy benefit	Not routinely supported
Add GnRH agonist?	Benefit signal; no ↑OHSS in cited meta-analysis	Potential adjuvant
Route	No clear superior route	Choose effective/tolerable regimen
Timing	Best window around OPU to +3 days	Avoid premature or delayed exposure
Serum P4	Both low and high levels associated with poorer outcome	Consider concentration, not dose alone

Greenbaum et al. 2022, pp. 2–3

Four FET pathways: the clinical map



Key discriminator

Does a functioning corpus luteum exist?

Greenbaum et al. 2022, Figure 2 & pp. 4

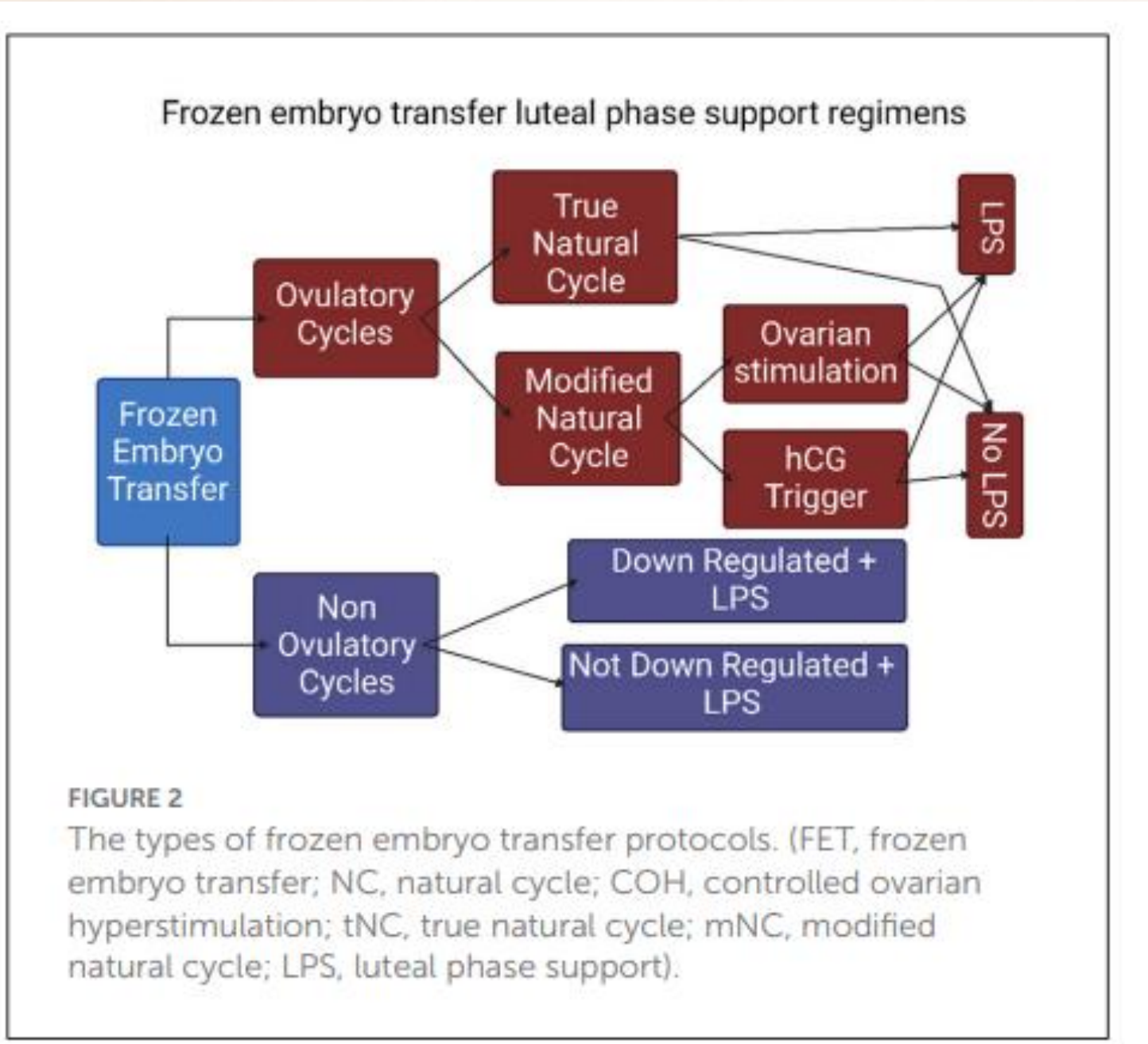
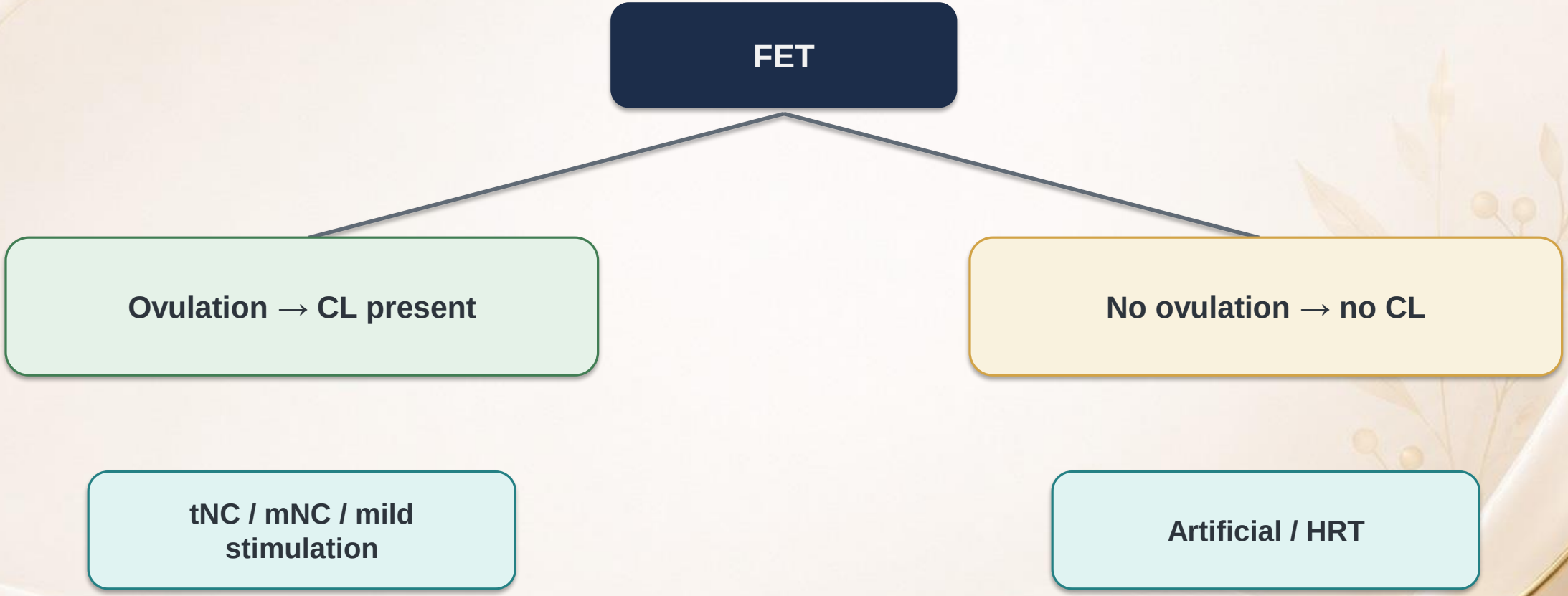


FIGURE 2

The types of frozen embryo transfer protocols. (FET, frozen embryo transfer; NC, natural cycle; COH, controlled ovarian hyperstimulation; tNC, true natural cycle; mNC, modified natural cycle; LPS, luteal phase support).

Greenbaum et al. 2022

FET: the decisive question is corpus luteum status



Greenbaum et al. 2022, pp. 4–5

Artificial / HRT FET: why progesterone is essential

- Artificial cycles are inherently non-ovulatory and therefore lack a functioning CL.
- Estrogen is used to achieve adequate endometrial proliferation and suppress follicular recruitment.
- Progesterone exposure then initiates decidualization and establishes the WOI.
- The embryo must be transferred after the correct duration of progesterone exposure.
- Therefore, progesterone timing is not simply “luteal support”—it is part of cycle synchronization.

Two goals of HRT preparation

1) Adequate endometrial proliferation. 2) Prevention of spontaneous follicular development/ovulation that could shift progesterone exposure.

Greenbaum et al. 2022, pp. 4
Yarali H, et al. Preparation of endometrium for frozen embryo replacement cycles: a systematic review and meta-analysis. J Assist Reprod Genet. (2016)

Estradiol in Programmed FET: Why Is It Continued?

Physiologic rationale for estrogen replacement in HRT-FET

- Programmed/HRT-FET cycles lack a functional corpus luteum; therefore, endogenous ovarian estradiol and progesterone secretion cannot be relied upon for endometrial and early-pregnancy support.
- Exogenous estradiol is used to proliferate and maintain the endometrium and is continued after progesterone initiation and embryo transfer in most HRT-FET protocols.
- After implantation, placental steroidogenesis progressively increases; however, the precise point at which endogenous/placental steroid production makes continued exogenous estradiol unnecessary is not clearly defined.
- Importantly, evidence for post-transfer E2 duration is much weaker than the evidence supporting progesterone luteal support.

CLINICAL PEARL • In programmed FET, E2 replacement is physiologically different from "add-on" estrogen in stimulated IVF cycles.

1. Ata B, et al. Expert opinion on best practice in programmed frozen embryo transfers: a Delphi consensus. Reprod Biomed Online. 2026;53(3):105820.
2. 2. Duration of estradiol supplementation in luteal phase support for frozen embryo transfer in hormone replacement treatment cycles: a randomized, controlled phase III trial. 2021.
3. 3. ESHRE Guideline: Ovarian Stimulation for IVF/ICSI – Update 2025.

Duration of Estradiol After a Positive Pregnancy Test

What does the evidence actually support?

TRADITIONAL PRACTICE

EMERGING EVIDENCE

2026 PERSPECTIVE

- E2 + progesterone continued after positive β-hCG.
- Commonly maintained until 10–12 weeks' gestation.

Randomized phase III trial: E2 stopped at ~6 weeks after confirmation of gestational sac + fetal heartbeat.

- No worsening of pregnancy outcomes was observed; study size was limited.

- Current evidence does not establish 10–12 weeks as a mandatory duration.
- Practice remains heterogeneous; individualized protocols are reasonable.

BOTTOM LINE • There is currently no high-quality evidence defining a single mandatory gestational age for stopping E2 in uncomplicated programmed FET pregnancies.

1. Ata B, et al. Expert opinion on best practice in programmed frozen embryo transfers: a Delphi consensus. Reprod Biomed Online. 2026;53(3):105820.
2. 2. Duration of estradiol supplementation in luteal phase support for frozen embryo transfer in hormone replacement treatment cycles: a randomized, controlled phase III trial. 2021.
3. 3. ESHRE Guideline: Ovarian Stimulation for IVF/ICSI – Update 2025.

Practical Estradiol Discontinuation Strategy

A pragmatic approach for uncomplicated HRT-FET pregnancy

β-hCG positive → **Confirm viable IUP + fetal cardiac activity** → **Continue E2 + P4 through early pregnancy** → **Consider E2 cessation ~8–10 wk***

HOW TO DISCONTINUE?

- No evidence demonstrates that a prolonged estrogen taper is required; a gradual dose reduction is therefore not clearly evidence-based.
- Once discontinuation is selected, E2 can generally be stopped according to the center's protocol rather than tapered over several weeks.
- Progesterone is a separate issue: do not assume that E2 and progesterone should be discontinued simultaneously.
- *8–10 weeks represents a pragmatic clinical window, NOT an evidence-mandated stopping point.

TAKE-HOME • Avoid presenting "stop E2 at 10–12 weeks" as a guideline-mandated rule. The evidence supports flexibility, not a single universal stopping week.

1. Ata B, et al. Expert opinion on best practice in programmed frozen embryo transfers: a Delphi consensus. Reprod Biomed Online. 2026;53(3):105820.
2. 2. Duration of estradiol supplementation in luteal phase support for frozen embryo transfer in hormone replacement treatment cycles: a randomized, controlled phase III trial. 2021.
3. 3. ESHRE Guideline: Ovarian Stimulation for IVF/ICSI – Update 2025.

True natural-cycle FET: do we need LPS?

- tNC FET occurs after spontaneous ovulation with an endogenous CL.
- The need for additional LPS is therefore less intuitive than in artificial cycles.
- The cited meta-analysis included 8 studies: 2 used hCG and 6 used progesterone.
- hCG LPS appeared non-beneficial.
- Progesterone LPS was associated with higher clinical pregnancy rate and live birth rate.

Pooled estimates for progesterone LPS

Clinical pregnancy: OR 1.48 (95% CI 1.14–1.94) • Live birth: OR 1.67 (95% CI 1.19–2.36)

Greenbaum et al. 2022,
Mizrachi et al. . Should women receive luteal support following natural cycle frozen embryo transfer? a systematic review and meta-analysis. Hum Reprod Update. (2021) . 2021

Modified natural-cycle FET: trigger changes the physiology

- mNC uses an hCG trigger to induce ovulation.
- Follicular development may be supported with aromatase inhibitors, clomiphene, or gonadotropins.
- Stimulation can occasionally result in more than one CL, strengthening the rationale for LPS.
- A small RCT found similar outcomes with vs without vaginal progesterone LPS.
- A retrospective study found lower miscarriage and higher LBR with LPS.

Evidence is mixed

RCT evidence and retrospective evidence are not fully concordant; pooled comparisons between tNC and mNC do not show a consistent outcome difference.

Horowitz E, , et al. A randomized controlled trial of vaginal progesterone for luteal phase support in modified natural cycle - frozen embryo transfer. Gynecol Endocrinol. (2021)
Kim CH, , et al. The effect of luteal phase progesterone supplementation on natural frozen-thawed embryo transfer cycles. Obstet Gynecol Sci. (2014)
Mackens S,et al. To trigger or not to trigger ovulation in a natural cycle for frozen embryo transfer: a randomized controlled trial. Hum Reprod. (2020)

tNC vs mNC: what do pooled data suggest?

Comparison	Pooled finding in cited meta-analysis	Interpretation
tNC vs mNC	No statistically significant difference in clinical pregnancy or LBR	Trigger strategy alone does not clearly determine outcome
tNC with LPS vs mNC	No consistent superiority	LPS practice may modify the comparison
Why studies differ	Some mNC protocols included ovarian stimulation	Protocol heterogeneity matters

Clinical message

Do not treat “natural” and “modified natural” as interchangeable protocols—the details of follicular stimulation, trigger, LH dynamics, and LPS matter.

Horowitz E, , et al. A randomized controlled trial of vaginal progesterone for luteal phase support in modified natural cycle - frozen embryo transfer. Gynecol Endocrinol. (2021)
Kim CH, , et al. The effect of luteal phase progesterone supplementation on natural frozen-thawed embryo transfer cycles. Obstet Gynecol Sci. (2014)
Mackens S,et al. To trigger or not to trigger ovulation in a natural cycle for frozen embryo transfer: a randomized controlled trial. Hum Reprod. (2020)

Artificial vs ovulatory FET: interpret with caution

Comparison	Reported pooled result	Important caveat
tNC vs AC without suppression	CPR favored tNC: OR 1.46 (1.07–1.99)	LBR difference not significant
tNC vs AC with suppression	LBR favored AC with suppression: OR 0.73 (0.56–0.95)	Sub-analysis influenced by single retrospective study
mNC + LPS vs AC without suppression	No significant difference	Protocol heterogeneity

Interpretation

These comparisons are heterogeneous and should not be read as proof that one FET preparation method is universally superior.

Greenbaum et al. 2022, pp. 4
Yarali H, et al. Preparation of endometrium for frozen embryo replacement cycles: a systematic review and meta-analysis. J Assist Reprod Genet. (2016)

Progesterone route in FET: the evidence shifts

- Daily IM progesterone(natural progesterone dissolved in oil) is considered the gold standard but is uncomfortable and rarely may cause sterile abscesses/infection.
- Vaginal progesterone offers convenience but may produce lower and more variable serum progesterone.
- Subcutaneous aqueous progesterone has shown two non-inferior RCTs compared 25 mg SC progesterone to micronized vaginal progesterone (MVP) in fresh ET and showed similar efficacy
- A retrospective study comparing SC to IM progesterone in AC FETs demonstrated similar outcomes
- In FET, recent RCTs cited in the review found higher serum progesterone with IM administration.
- A large RCT (1,125 FET cycles) demonstrated higher LBR with daily IM progesterone than vaginal progesterone alone.

Greenbaum et al. 2022, pp.
Lockwood G, et al. Subcutaneous progesterone versus vaginal progesterone gel for luteal phase support in in vitro fertilization: a noninferiority randomized controlled study. Fertil Steril. (2014)
Haddad G, et al. Intramuscular route of progesterone administration increases pregnancy rates during nondownregulated frozen embryo transfer cycles. J Assist Reprod Genet. (2007)
Hershko Klement A, , et al. Intramuscular versus vaginal progesterone administration in medicated frozen embryo transfer cycles: a randomized clinical trial assessing sub-endometrial contractions. Gynecol Obstet Invest. (2018)

The 1,125-cycle randomized trial: IM vs vaginal

Outcome	IM progesterone	IM q3d + vaginal	Vaginal only
Clinical pregnancy rate	57%	56%	39%
Pregnancy loss	33%	26%	52%
Live birth rate	46%	48%	29%

Study-level conclusion

The vaginal-only arm was discontinued after interim analysis because of poorer outcome; combined IM + vaginal had similar LBR to daily IM.

Devine K, et al. Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial. Fertil Steril. (2021)

IM progesterone: efficacy vs tolerability

Potential advantage

Higher serum progesterone and, in cited RCT evidence, higher live birth rate.

Main disadvantage

Daily injections are painful/discomforting and rarely may cause sterile abscess or infection.

Alternative

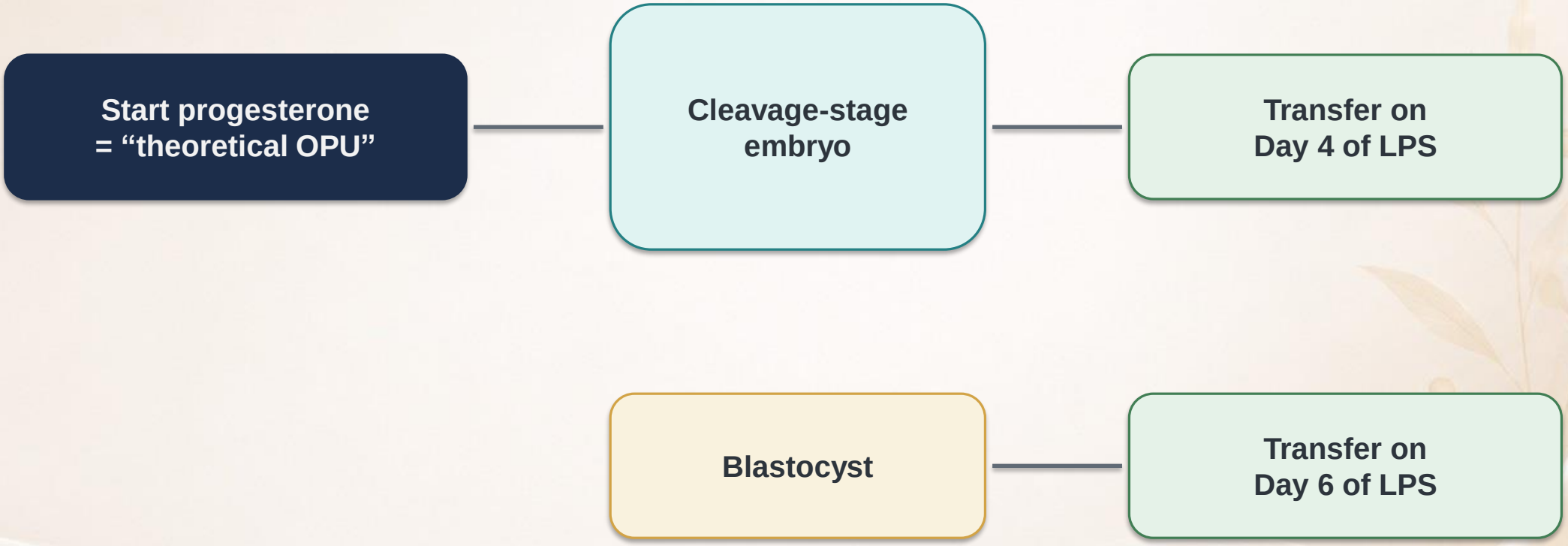
IM every 3 days + vaginal progesterone was reported as non-inferior to daily IM in one cited study.

Clinical decision

Route selection should integrate efficacy, serum P4, adherence, tolerability, and the specific FET protocol.

Greenbaum et al. 2022, p. 5

Timing progesterone in artificial FET: the embryo clock



Greenbaum et al. 2022, pp.
Mackens S, et al. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. Hum Reprod. (2017)
Noble M, et al, editors. Natural Cycle Frozen-Thawed Embryo Transfer (FET): A Comparison of Outcomes Following Blastocyst Transfer on Day Six Versus Day Seven After Urinary Luteinising Hormone (LH) Surge. ESHRE (2020)

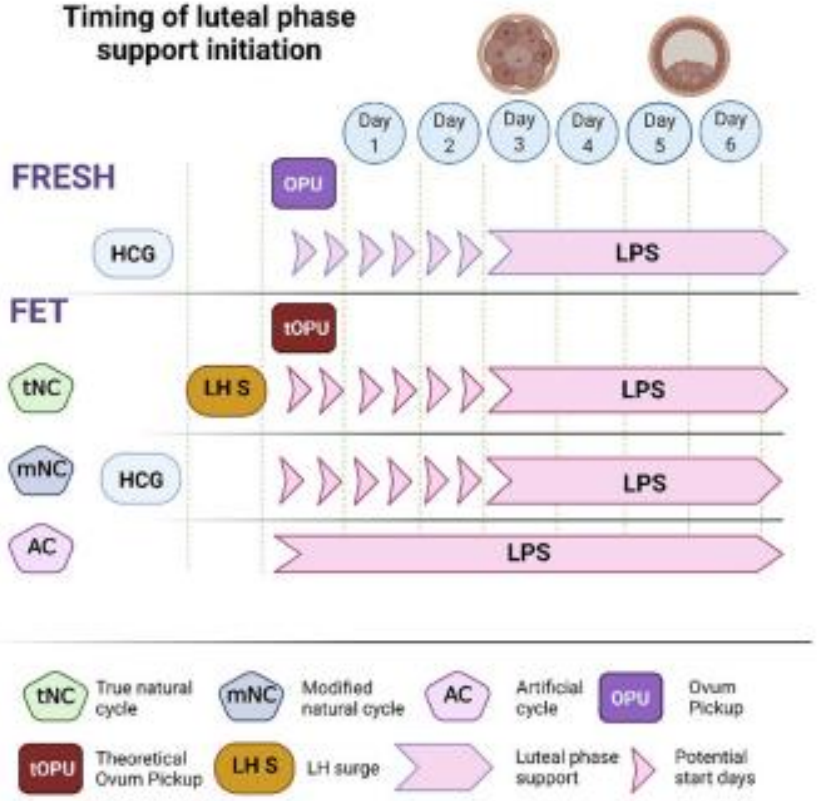


FIGURE 1

The optimal range of LPS initiation during fresh and frozen embryo transfer. In fresh cycles the optimal range of LPS initiation was defined as day of OPU and up to 3 days later. In frozen transfers, the start of LPS depends on the presence of a corpus luteum (CL). In artificial cycles that take place in the absence of a CL, the transfer of a day 3 embryo and a blastocyst should be performed on the 4th and 6th days of LPS, respectively. In natural and modified natural FETs we refer to a theoretical OPU to standardize the optimal range of LPS initiation. Embryo transfer should be performed 1 day sooner following an LH surge in a tNC, compared to hCG trigger in a mNC.

Greenbaum et al. 2022

What is “theoretical OPU” in FET?

- FET has no actual oocyte retrieval, so a reference point is needed to compare progesterone exposure across protocols.
- “Theoretical OPU” is defined from embryo age at vitrification minus one day.
- This framework allows timing to be translated between fresh and frozen cycles.
- The clinical goal is the same: synchronize progesterone exposure with embryo developmental age.

Why it matters

A blastocyst is not simply transferred “six days after starting progesterone” in isolation—the timing is meaningful because it recreates the embryo–endometrium developmental relationship.

Greenbaum et al. 2022, pp.
Mackens S, et al. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. Hum Reprod. (2017)
Noble M, et al, editors. Natural Cycle Frozen-Thawed Embryo Transfer (FET): A Comparison of Outcomes Following Blastocyst Transfer on Day Six Versus Day Seven After Urinary Luteinising Hormone (LH) Surge. ESHRE (2020)

Natural FET timing: LH surge vs hCG trigger

True natural cycle
LH surge

Modified natural cycle
hCG trigger

ET timing

Physiology

After LH surge, spontaneous ovulation occurs ~24–56 h later and is preceded by a preovulatory progesterone rise.

Trigger difference

hCG-triggered cycles may lack the same preovulatory progesterone rise.

Timing deduction

ET should occur 1 day earlier after an LH surge than after an hCG trigger.

Greenbaum et al. 2022, pp.
Mackens S, et al. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. Hum Reprod. (2017)
Noble M, et al, editors. Natural Cycle Frozen-Thawed Embryo Transfer (FET): A Comparison of Outcomes Following Blastocyst Transfer on Day Six Versus Day Seven After Urinary Luteinising Hormone (LH) Surge. ESHRE (2020)

The LH+6 vs LH+7 natural FET signal

Policy change(A retrospective study by Noble et al. (39) presented at the ESHRE conference in 2020)

Blastocyst transfer changed from LH+7 to LH+6 in the cited retrospective dataset.

Timing	Adjusted ongoing pregnancy >24 weeks
LH+7	29%
LH+6	45%
Adjusted OR	2.13 (95% CI 1.44–3.14), p < 0.0001

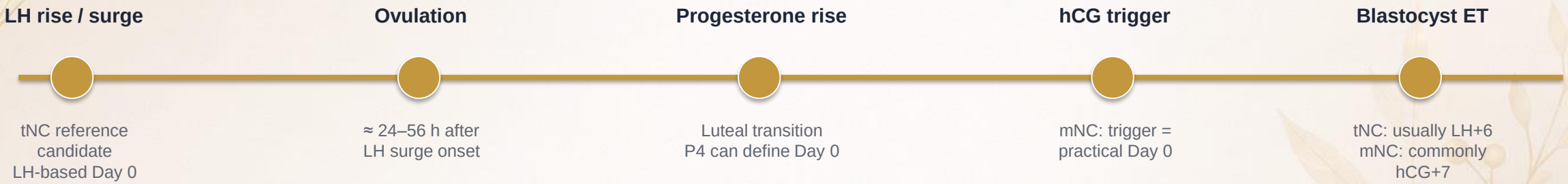
Important caveat

This was retrospective conference data, not an RCT. The AC comparison in the same periods did not show a significant change.

Greenbaum et al. 2022, pp.
Mackens S, et al. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. Hum Reprod. (2017)
Noble M, et al, editors. Natural Cycle Frozen-Thawed Embryo Transfer (FET): A Comparison of Outcomes Following Blastocyst Transfer on Day Six Versus Day Seven After Urinary Luteinising Hormone (LH) Surge. ESHRE (2020)

Defining “Day 0” in Natural & Modified-Natural FET

Practical endocrine framework for blastocyst transfer — the reference day must be defined BEFORE assigning ET timing



TRUE NATURAL CYCLE (tNC)

- LH-based: LH surge day = Day 0 → blastocyst ET usually LH+6
- No universal LH-surge definition; reported thresholds vary
- 2025 data support integrating LH + E2 + P4 rather than LH alone
- Alternative: P4-based luteal-day assignment can schedule ET by estimated luteal age

PROGESTERONE-BASED tNC

- A 2026 prospective cohort used the first P4 ≥1.0 ng/mL as luteal transition
- P4 1.0–1.6 ng/mL → estimated Day 0
- P4 1.6–2.6 → Day 1; 2.6–5.0 → Day 2
- Blastocyst ET targeted to estimated luteal Day 5
- Live birth comparable with LH-timed scheduling

MODIFIED NATURAL CYCLE (mNC)

- hCG trigger is the operational Day 0
- Conventional blastocyst timing: hCG+7
- New 2026 multicentre RCT: Day 6 vs Day 7 showed similar LBR
- If spontaneous LH surge is present, some protocols advance ET to hCG+6
- Therefore: document the trigger day AND whether endogenous LH has already risen

KEY CLINICAL POINT: “Day 0” is a protocol-defined endocrine reference point — not necessarily the exact moment of follicular rupture.

Key references: Orvieto et al., J Ovarian Res 2025; Aydin et al., Hum Reprod 2026; Saupstad et al., Hum Reprod Open 2026; Mumusoglu et al., Hum Reprod Update 2022.

Recent Evidence: How Should We Define Day 0?

Comparative evidence for LH-, progesterone-, and hCG-based reference days in NC-FET / mNC-FET

Study	Design / N	Protocol	Day 0 definition	ET timing	Main finding	Year
Orvieto et al. J Ovarian Res	Retrospective 668 NC-FET	tNC	LH rise + E2 fall + ~3-fold P4 rise (D−2→D−1)	Protocol-specific; focus = identifying surge	Pregnancy cycles showed a greater peri-ovulatory P4 rise; authors propose combined endocrine definition	2025
Aydin et al. Hum Reprod	Prospective cohort 490 tNC-FET	tNC	P4-based luteal age: ≥1.0 ng/mL; 1.0–1.6 = D0	Estimated luteal D5 for blastocyst	LBR 56.6% P4-timed vs 52.0% LH-timed; adjusted RR 1.09 (95% CI 0.93–1.30)	2026
Saupstad et al. Hum Reprod Open	Multicentre RCT 602 transfers	mNC	hCG trigger = Day 0	Blastocyst ET Day 6 vs Day 7	LBR: 33.8% vs 33.0%; aRD −0.62% (95% CI −7.99 to 6.75), P=.87	2026

PRACTICAL TAKE-HOME

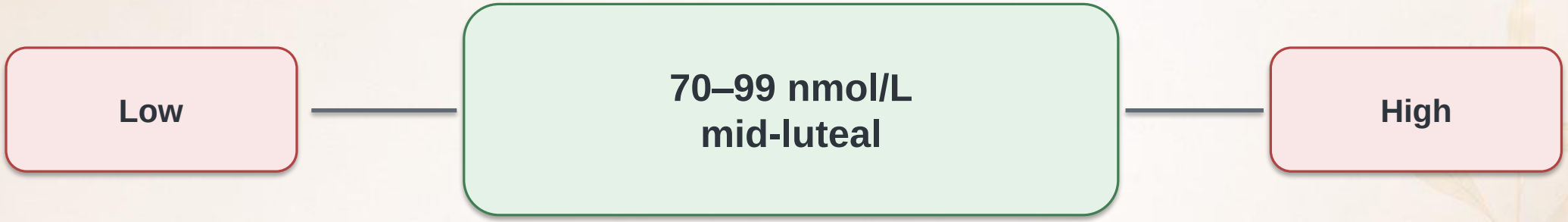
tNC: choose ONE reproducible endocrine reference (LH or P4) and apply the same convention consistently.

mNC TAKE-HOME

hCG = Day 0 remains the operational standard; current RCT data suggest Day 6 and Day 7 blastocyst transfer are both viable scheduling windows.

References: Orvieto R et al. J Ovarian Res. 2025;18:77. doi:10.1186/s13048-025-01658-7. Aydin T et al. Hum Reprod. 2026;41:1581–1590. doi:10.1093/humrep/deag109. Saupstad M et al. Hum Reprod Open. 2026;2026:hoag003. doi:10.1093/hropen/hoag003. Erden M et al. Hum Reprod. 2022.

Serum progesterone in FET: an optimal zone



Study message

Serum progesterone on the day of FET correlated with CPR and LBR; both below and above the mid-luteal range were associated with poorer outcomes.
The effect of serum progesterone concentration was independent of embryo grading, body mass index or the woman's age, either at vitrification or at FET

— Greenbaum et al. 2022,
Yovich JL, et al. Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement. Reprod Biomed Online. (2015)

Can we rescue low progesterone on transfer day?

Study / strategy	Low P4 definition	Intervention	Outcome signal
Gao et al.(2021) China	<10 ng/mL	40 mg IM progesterone	CPR and LBR remained lower
Labarta et al.(2022) Spain	<9.2 ng/mL	25 mg SC added to 400 mg vaginal BID	LBR 44.9% vs 37.3%; OR 1.37 (1.06–1.78)

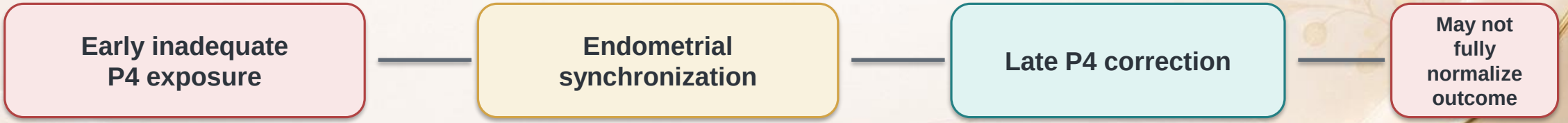
Interpretation

Rescue may help in some cohorts, but definitions of “low P4” and rescue regimens differ; the review calls for a large well-designed RCT.

Gao H, et al Strengthened luteal phase support for patients with low serum progesterone on the day of frozen embryo transfer in artificial endometrial preparation cycles: a large-sample retrospective trial. Reprod Biol Endocrinol. (2021)
Labarta E, et al. Individualized luteal phase support normalizes live birth rate in women with low progesterone levels on the day of embryo transfer in artificial endometrial preparation cycles. Fertil Steril. (2022)

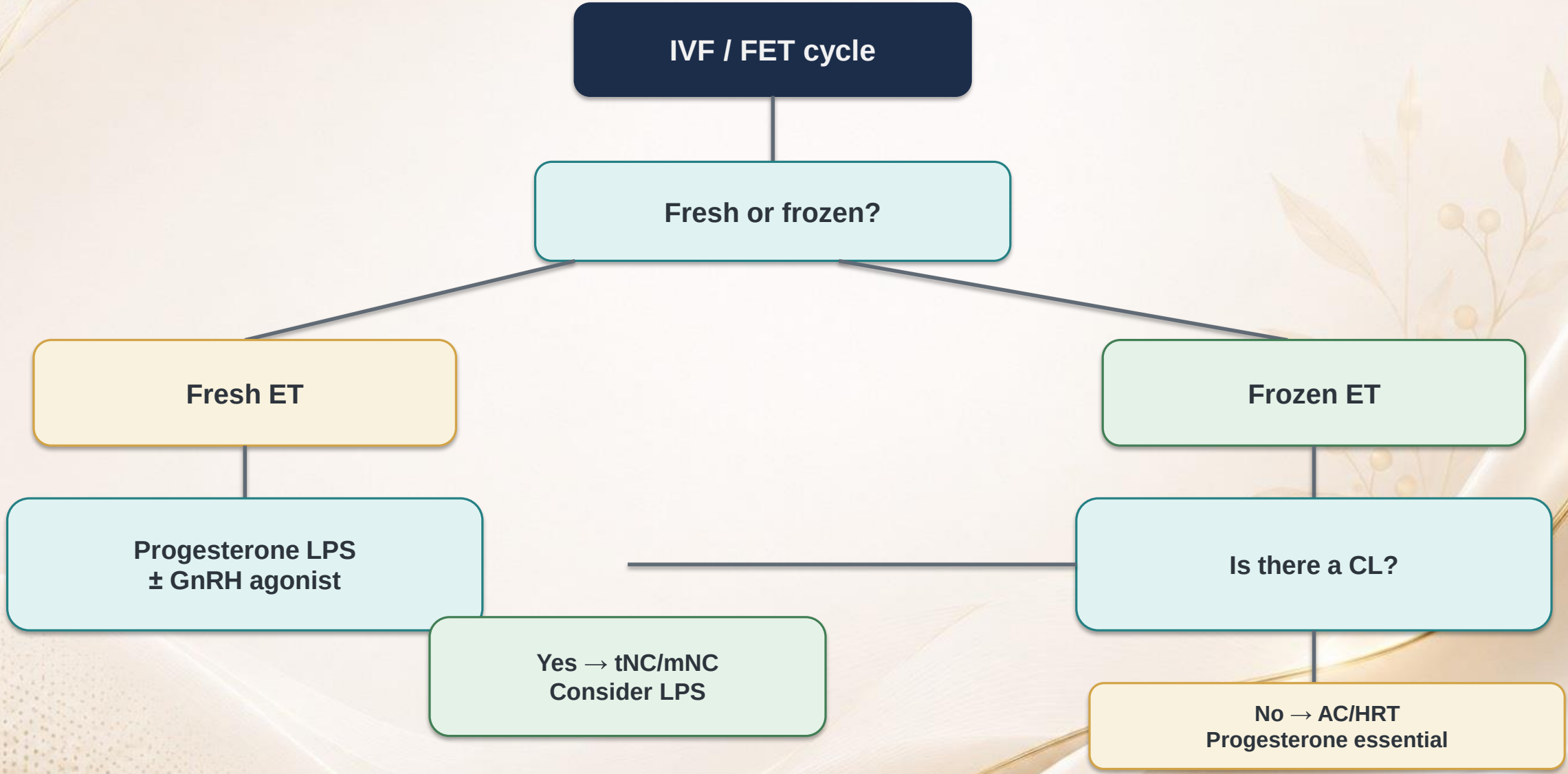
Why correction of low P4 may not fully rescue outcome

- Low serum progesterone on the day of transfer may reflect inadequate exposure earlier in the luteal phase.
- Correcting the concentration later may not completely reverse an already altered secretory transformation.
- The review proposes that abnormal endometrial synchronization could explain incomplete rescue.
- This supports monitoring and protocol quality—not only reacting to a low number on transfer day.



Gao H, et al Strengthened luteal phase support for patients with low serum progesterone on the day of frozen embryo transfer in artificial endometrial preparation cycles: a large-sample retrospective trial. Reprod Biol Endocrinol. (2021)

Clinical algorithm: choosing luteal support



Synthesized from Greenbaum et al. 2022

Fresh vs frozen: the evidence at a glance

Domain	Fresh ET	Frozen ET
Progesterone LPS	Supported	Supported
hCG add-on	No benefit; ↑OHSS	Not favored as routine tNC support
Estradiol add-on	No demonstrated benefit	Part of artificial-cycle endometrial preparation
GnRH agonist	Potential adjuvant benefit	Protocol-dependent
IM vs vaginal	No clear superiority	IM favored in cited programmed-FET RCT evidence
Timing	OPU → up to ~3 days	Depends on protocol; embryo age + progesterone exposure are critical
Serum P4	Both low/high associated with poorer outcome	Mid-luteal optimal zone reported; low P4 may require individualized strategy

Greenbaum et al. 2022, Conclusions

When Can We Stop Progesterone Luteal Support?

Fresh IVF/ICSI cycles • Evidence for early versus extended progesterone

Key message: Extended progesterone has not consistently improved live birth or ongoing pregnancy outcomes.

Study	Design / N	Early-stop strategy	Extended strategy	Main finding
Kohls et al., 2012	RCT • n=220	Stop at 5 weeks	Continue to 8 weeks	No significant difference in pregnancy/miscarriage outcomes; early-stop group had more bleeding.
Watters et al., 2020	SR/MA • 7 RCTs • n=1,627	Various early regimens	Extended LPS	No significant difference in LBR (RR 0.94), miscarriage (RR 0.91) or ongoing pregnancy (RR 0.98).
Mizrachi et al., 2020	Literature review	Some studies: positive β-hCG	Often ≥8 weeks	Most studies showed no clear benefit from extension, but evidence was insufficient for a universal early-stop policy.
ESHRE Guideline Update, 2025	Guideline	—	—	Current recommendation: progesterone should be administered at least until the day of the pregnancy test.

Clinical interpretation | Early cessation may be reasonable in selected protocols, but it is not yet the universal guideline standard.

Kohls et al. Fertil Steril. 2012;98:858–862. | Watters et al. RBMO. 2020;40:143–150. | Mizrachi et al. Front Reprod Health. 2020;2:610532. | ESHRE Guideline Update 2025.

Practical Take-Home: How Long Should LPS Continue?

A clinically useful framework for IVF/ICSI • Do not extrapolate automatically to IUI or FET

Oocyte retrieval
Day 0

Embryo transfer
Day 2–5

β-hCG test
~10–14 days

Pregnancy US
~5–6 weeks

Luteo-placental shift
~8–10 weeks

IVF/ICSI

- ESHRE 2025: continue progesterone at least until the day of the pregnancy test.
- Meta-analysis: prolonged LPS did not show a consistent benefit for live birth.
- Stopping after a positive test has been studied, but evidence remains heterogeneous.
- Therefore, avoid presenting 5–8 weeks as a universally proven stopping point.

IMPORTANT LIMITATIONS

- Evidence mainly comes from fresh IVF/ICSI cycles.
- Do not directly extrapolate these data to every FET or IUI protocol.
- Kohls RCT: early cessation was associated with more bleeding.
- The optimal stopping time may depend on stimulation, trigger and luteal function.

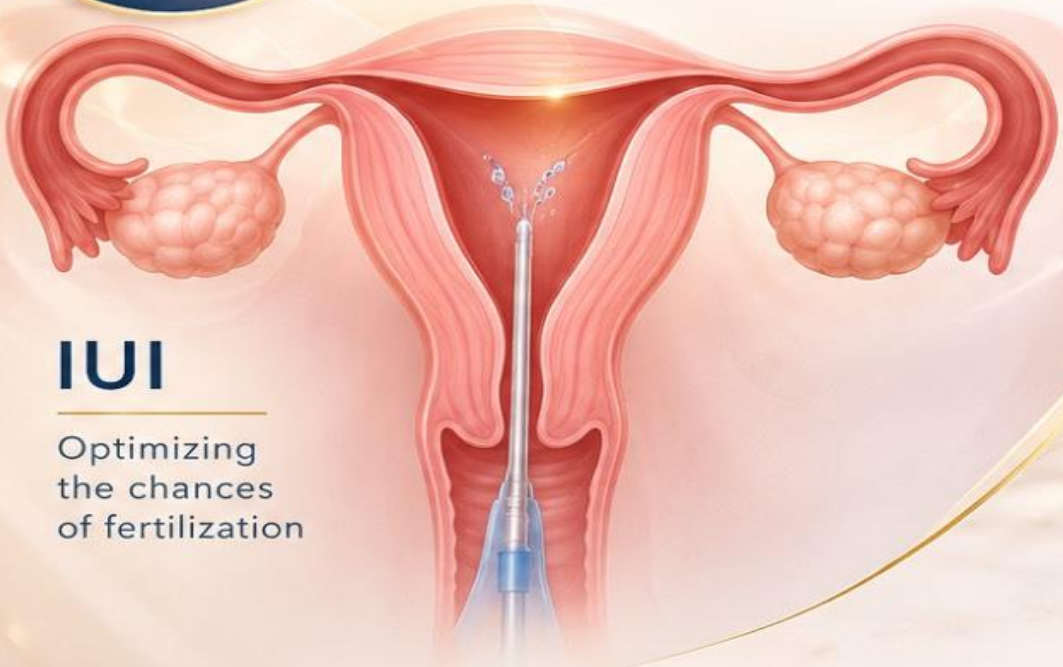
BOTTOM LINE | Current ESHRE guidance = progesterone through the pregnancy test; evidence does not support routine unnecessary prolongation beyond that point.

ESHRE Guideline: Ovarian Stimulation for IVF/ICSI – Update 2025. Human Reproduction. 2026. | Watters et al. 2020. | Kohls et al. 2012.



IUI & Luteal Phase Support

Better Timing • Stronger Support • Higher Chances



IUI

Optimizing the chances of fertilization

Luteal Phase Support

Maintaining the endometrium for implantation and early pregnancy

Progesterone

hCG

Estrogen





From Ovulation to Implantation

1. Why luteal support is considered in IUI

• IUI(Intrauterine insemination) places prepared sperm directly into the uterine cavity to increase the number of healthy sperm reaching the fertilization site.

• Controlled ovarian stimulation (COS) is used to increase oocyte number, correct occult ovulatory disorders and optimize insemination conditions.

- IUI is widely used for conditions such as **mild male-factor infertility, unexplained infertility, and minimal or mild endometriosis**.
- it is less costly than IVF/ICSI, its pregnancy rate per cycle is generally lower.
- The effectiveness of IUI depends on several factors, including the indication, ovarian stimulation protocol, number of follicles, sperm preparation technique, insemination timing, prevention of premature LH surges, and adequacy of the luteal phase.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016
ESHRE Capri Workshop Group. Intrauterine insemination. Hum Reprod Update 2009;

1. Why luteal support is considered in IUI

- A major unresolved issue is the role of **luteal phase support (LPS)** in stimulated IUI cycles.
- Current evidence suggests that **luteal phase supplementation may be beneficial in gonadotropin-stimulated IUI cycles, particularly when multiple follicles develop**
- Stimulation may produce multifollicular development and supraphysiologic estradiol concentrations.
- These steroid changes can suppress the hypothalamic–pituitary axis and impair the LH pattern required for optimal corpus luteum function.
- Observed consequences include a shortened luteal phase and abnormal early-luteal endometrial progression.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016
ESHRE Capri Workshop Group. Intrauterine insemination. Hum Reprod Update 2009;

2. Biological rationale: COS → luteal dysfunction → implantation concern

COS / multifollicular growth

Multiple follicles → supraphysiologic estradiol → negative feedback on the hypothalamic–pituitary axis.

LH environment

Reduced/altered LH oscillation may compromise corpus luteum function and contribute to defective progesterone support.

Progesterone

Progesterone supports early pregnancy and implantation and produces secretory transformation of the endometrium.

Endometrium

Ovarian stimulation was associated with abnormal early-luteal endometrial progression in ~50% of cases in the cited observational work.

- Observational studies cited in the review found the luteal phase after gonadotropin stimulation to be ~20% shorter, with an average duration of 11 days.
- Mid-luteal hCG can normalize luteal-phase length and increase mid-luteal progesterone, but serum progesterone alone does not reliably define luteal function.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016
Fatemi HM, ET AL. An update of luteal phase support in stimulated IVF cycles. Hum Reprod Update 2007
Fauser BC, ET AL. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab 2003;

3. Premature LH surge in stimulated IUI

Definition in the review

Premature LH rise >10 IU/L accompanied by a progesterone rise >1 mg/L (3.2 nM/L).

Frequency

Reported in stimulated IUI cycles at approximately 25–30%.

Clinical relevance

May lead to cycle cancellation or treatment failure.

- An LH surge is physiologically required for follicular rupture and oocyte maturation.
- GnRH antagonists can prevent premature LH rises, but the cited evidence did not show improved pregnancy rates—suggesting that the problem is not explained solely by early luteinization/premature LH surge.
- The review therefore frames luteal support as a separate question: can progesterone supplementation improve outcomes after stimulated IUI?

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016;
Tavaniotou A, ET AL. Comparison of LH concentrations in the early and mid-luteal phase in IVF cycles after HMG alone or in association with GnRH antagonist Cetrorelix. Hum Reprod 2001
Tavaniotou A, ET AL. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. Fertil Steril 2003

4. Randomized evidence: progesterone after IUI

Erdem et al., 2009

rFSH-stimulated IUI; vaginal progesterone gel 90 mg/day starting 2 days after IUI. CPR/cycle: 21.1% vs 12.7% (p=0.028). LBR/cycle: 17.4% vs 9.3% (p=0.016).

Maher, 2011

rFSH-stimulated IUI; vaginal progesterone gel 90 mg/day for 14 days. LBR/cycle: 18.9% vs 5.5% (p<0.001); CPR difference did not reach significance (29.5% vs 19.8%, p=0.07).

Agha-Hosseini et al., 2012

Mixed stimulation regimens. Vaginal progesterone 400 mg/day. CPR: 24.3% vs 14.1% (p=0.02); BPR difference NS.

- Across the RCTs summarized in the review, vaginal progesterone was the luteal-support strategy used.
- Not every individual trial demonstrated benefit; effects varied by stimulation protocol and outcome.
- Multiple pregnancy and miscarriage rates were not significantly different between support and no-support groups in the pooled RCT literature.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016;13:90–94 | 5/8

5. Meta-analyses: overall signal favors luteal support

Hill et al. (2013) — systematic review/meta-analysis

Clinical pregnancy: OR 1.47 (95% CI 1.15–1.98)
Live birth: OR 2.11 (95% CI 1.21–3.67)

Miralpeix et al. (2014) — systematic review/meta-analysis

Clinical pregnancy: RR 1.41 (95% CI 1.14–1.76)
Live birth: RR 1.94 (95% CI 1.36–2.77)

- Both meta-analyses found significantly higher clinical pregnancy and live birth outcomes with luteal support.
- Subgroup analyses suggested that the benefit was concentrated in gonadotropin-stimulated IUI cycles rather than all stimulation settings.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016;13:90–94 | 6/8

Luteal Phase Support in IUI Cycles

Randomized controlled trials: stimulation protocols, progesterone regimens and assessed outcomes

Study	Patients	Tx / Control cycles	Stimulation	Luteal support (dose & duration)	Outcomes
Erdem et al., 2009	214	223 / 204	rFSH	Vaginal progesterone gel 90 mg/24 h, once daily → 12 wk	CPR, BPR, LBR, MPR, MR
Kyrou et al., 2010	468	196 / 204	Clomiphene citrate	Vaginal progesterone suppositories 200 mg/8 h → 7 wk	CPR, BPR, MPR, MR
Ebrahimi et al., 2010	200	252 / 259	Clomiphene citrate + hMG	Vaginal progesterone suppositories 400 mg/24 h, once daily → 10 wk	CPR, BPR, LBR, MPR, MR
Maher, 2011	71	132 / 126	rFSH	Vaginal progesterone gel 90 mg/24 h, once daily → 14 d	CPR, BPR, LBR, MPR, MR
Agha-Hosseini et al., 2012	300	148 / 142	Clomiphene citrate; CC + hMG; Letrozole + hMG	Vaginal progesterone suppositories 400 mg/24 h, once daily → 12 wk	CPR, BPR, MPR, MR
Hossein Rashidi et al., 2014	253	NA	Clomiphene citrate + hMG	Vaginal progesterone suppositories 400 mg/12 h, twice daily → 8 wk	CPR, BPR, MR
Khosravi et al., 2015*	150	NA	Clomiphene citrate + FSH	Vaginal progesterone suppositories 400 mg/24 h, once daily	CPR, MR

CPR, clinical pregnancy rate; BPR, biochemical pregnancy rate; LBR, live birth rate; MPR, multiple pregnancy rate; MR, miscarriage rate.

Reproductive Outcomes of Luteal Phase Support

Pregnancy outcomes reported in randomized controlled trials of IUI

Study	BPR (%) (p)	CPR (%) (p)	LBR (%) (p)
Erdem et al., 2009	25.1 vs 13.7 (0.002)	21.2 vs 12.7 (0.028)	17.4 vs 9.3 (0.016)
Kyrou et al., 2010	—	7.3 vs 8.7 (NS)	—
Ebrahimi et al., 2010	13.5 vs 11.2 (NS)	11.5 vs 10.0 (NS)	7.5 vs 5.7 (NS)
Maher, 2011	37.1 vs 20.6 (0.004)	29.5 vs 19.8 (0.07)	18.9 vs 5.5 (<0.001)
Agha-Hosseini et al., 2012	29.0 vs 21.8 (NS)	24.3 vs 14.1 (0.02)	—
Hossein Rashidi et al., 2014	30.8 vs 22.2 (NS)	15.8 vs 12.7 (NS)	—
Khosravi et al., 2015*	—	25.7 vs 29.7 (NS)	—

KEY MESSAGE • Benefit of luteal support was not uniform across trials; several studies reported significantly higher pregnancy outcomes, while others showed no significant difference.

Data are presented as percentage rates in luteal-support vs no-support groups. NS = not significant. *See original table footnote for progesterone regimen.

6. The follicle-number question: where may benefit be greatest?

Mild stimulation: 1–2 follicles

ESHRE Capri Workshop Group (2009), based on six RCTs / 456 patients, stated that luteal support was not a major requisite for mild gonadotropin-stimulation IUI yielding 1–2 follicles.

>1 dominant follicle

Seckin et al. (2014) reported higher clinical pregnancy per patient with LPS in multifollicular cycles: 28.2% vs 11.4% (p=0.04).

- Interpretation: follicular response may modify the value of luteal support.
- The review's central conclusion is strongest for gonadotropin-stimulated IUI cycles producing more than one follicle.
- However, the authors emphasize that the available trials did not consistently report outcomes stratified by follicle number.

Based on Gün I, Özdamar Ö, Yılmaz A. Turk J Obstet Gynecol. 2016
ESHRE Capri Workshop 2009

hCG for Luteal Phase Support in IUI

Mechanism, studied regimens and interpretation of the evidence

WHY hCG?

- hCG activates LH receptors in the corpus luteum
- Supports endogenous progesterone secretion
- Biologically attractive after hCG-triggered ovulation
- Evidence is much less robust than the biologic rationale

REGIMENS REPORTED IN IUI LITERATURE

- 1,500 IU: low-dose luteotropic support reported in some protocols
- 2,500 IU: additional luteal dose reported in selected studies
- 5,000 IU: commonly used as the ovulation trigger; not synonymous with LPS

⚠ These are studied regimens—not a universal standard dose.

Trigger → Corpus luteum → hCG/LH-receptor stimulation → ↑ Progesterone → Endometrial support

Clinical caveat: repeated hCG exposure can increase luteal stimulation and OHSS risk, particularly in multifollicular gonadotropin-stimulated cycles.

van der Linden et al., Cochrane 2015; Cochrane IUI LPS review 2022.

hCG Luteal Support in IUI — What Do the Studies Show?

Selected evidence and how to interpret it accurately

Evidence	Population / comparison	hCG strategy	Main interpretation
Cochrane 2022	25 RCTs; 5,111 IUI participants overall	hCG vs no treatment; 1 RCT, n=130	Clinical pregnancy RR 0.93 (95% CI 0.40–2.13); very uncertain
Cochrane 2015	Assisted reproduction; hCG vs placebo/no support	Multiple hCG regimens	Possible benefit for ongoing pregnancy/live birth, but low/very-low certainty
Cochrane 2015	Progesterone vs hCG regimens	16 RCTs; 2,162 women	No clear difference in LBR/ongoing pregnancy; progesterone had less OHSS

Take-home: hCG is physiologically plausible, but current IUI evidence does not establish superiority over progesterone.

van der Linden et al., Cochrane CD012396 (2022); van der Linden et al., Cochrane CD009154 (2015).

hCG vs Progesterone for LPS in IUI

Parameter	hCG	Progesterone
Mechanism	LH-receptor stimulation → endogenous CL progesterone	Direct progesterone supplementation
Evidence in IUI	Limited; hCG vs no support: very uncertain	Better evidence, especially after gonadotropin OS-IUI
Clinical pregnancy / live birth	No convincing superiority	Meta-analyses show benefit vs no LPS/placebo in gonadotropin IUI
OHSS	Concern with repeated dosing	Lower OHSS risk than hCG regimens
Best framing	Selected cycles; not a universal standard	More established LPS option in stimulated IUI

Bottom line: In IUI, progesterone has the stronger clinical evidence base; hCG may be considered as a selected luteotropic strategy, with OHSS risk considered.

Groen et al., Fertil Steril 2017;
ESHRE et al., Front Endocrinol 2022;
Cochrane 2022.

7. Practical synthesis & take-home messages

- Consider luteal-phase progesterone support particularly after gonadotropin-stimulated IUI when >1 follicle develops.
- Vaginal progesterone is the principal route evaluated in the RCTs summarized by this review; doses and durations varied substantially.
- Evidence suggests improved clinical pregnancy and live birth rates overall, but benefit is not uniform across all stimulation protocols.
- Oral dydrogesterone was reported as a potentially effective alternative to vaginal progesterone in one randomized trial, without a statistically significant difference in clinical pregnancy or miscarriage.

ESHRE Capri Workshop 2009;
Erdem 2009; Hill 2013;
Miralpeix 2014; Seckin 2014
Gün et al. 2016.

Evidence Update: Luteal Phase Support in Ovulation Induction

Does every OI cycle need progesterone? • Focus: timed intercourse & IUI

Study	Design / population	Intervention	Key outcome	Interpretation
Green et al., 2017	11 RCTs • 2,842 pts 4,065 cycles	Progesterone after IUI	Gonadotropin-IUI: LBR RR 1.77 (1.30–2.42)	Benefit mainly with GONADOTROPIN-IUI
Casarramona et al., 2022	12 RCTs • 2,631 pts 3,262 cycles	LPS vs no LPS OS-IUI	Overall LBR RR 1.38 (1.09–1.74)	Supports LPS in stimulated IUI
Dilday et al., 2023	492 letrozole cycles 273 patients	Vaginal P4 vs none ± IUI/TIC	Clinical pregnancy: 11.6% vs 13.3%	No clear benefit; observational data
Xi et al., 2024	1,199 letrozole-IUI cycles	LPS vs no LPS	LBR 19.7% vs 14.5% (P=0.0255)	Suggests benefit, but non-randomized
AOGS, 2024	66 RCTs • 16,305 pts IUI add-ons	Vaginal P4 in stimulated IUI	LBR/ongoing pregnancy RR 1.37 (1.09–1.72)	Benefit probable; certainty limited

Bottom line: Evidence is strongest for gonadotropin-IUI; evidence for oral OI (especially TIC) is inconsistent.

Refs: Green 2017 • Casarramona 2022 • Dilday 2023 • Xi 2024 • AOGS 2024

Clinical Algorithm: Does This OI Cycle Need Luteal Support?

Protocol-specific approach based on the available evidence

OVULATION INDUCTION CYCLE

Timed intercourse (TIC)
Letrozole / Clomiphene
→ Routine LPS: NOT established
NO routine LPS

Oral OI + IUI
Letrozole / Clomiphene
→ Evidence mixed
INDIVIDUALIZE

Gonadotropin + IUI
Strongest OI evidence
→ Benefit in meta-analyses
LPS FAVORED

If this is IVF/ICSI → separate evidence base → routine progesterone LPS is recommended

KEY MESSAGE: "Luteal support should be protocol-specific, not procedure-specific."

ESHRE 2025: Luteal Phase Support After IVF/ICSI

Core recommendations — what should we do routinely?

1 PROGESTERONE IS RECOMMENDED

- Progesterone is recommended for luteal phase support after IVF/ICSI.
- Strength: STRONG recommendation (⨁○○○).
- Natural progesterone: non-oral routes can be used.
- 2025 update: this core recommendation is carried forward from 2019.

2 WHEN TO START & HOW LONG?

- Start between the evening of oocyte retrieval and Day 3 post-retrieval.
- Continue at least until the day of the pregnancy test.
- Evidence does not establish a clear live-birth advantage for very early vs later cessation.
- Practical message: use a consistent clinic protocol.

Source: ESHRE Guideline on Ovarian Stimulation for IVF/ICSI — 2025 update

ESHRE 2025: Routes & Common Natural Progesterone Doses

Administration is flexible — choose a validated non-oral regimen and maintain protocol consistency.

COMMON REGIMENS LISTED BY ESHRE (GPP)

- IM progesterone: 50 mg once daily
- SC progesterone: 25 mg once daily
- Vaginal progesterone gel: 90 mg once daily
- Micronized vaginal progesterone in-oil capsules: 200 mg three times daily
- Micronized vaginal progesterone in starch suppositories: 100 mg two or three times daily
- Vaginal pessary: 400 mg twice daily
- Key point: ESHRE does not identify one single route as universally superior.

Source: ESHRE Guideline on Ovarian Stimulation for IVF/ICSI — 2025 update

ESHRE 2025: What Is NOT Routinely Recommended?

Avoid adding hormonal 'extras' without evidence of benefit.

NOT RECOMMENDED / NOT ROUTINE

- Estradiol + progesterone: probably NOT recommended.
- hCG 1500 IU as luteal support in hCG-triggered stimulation cycles: NOT recommended.
- Adding LH activity to progesterone: research only / clinical trial context.
- Do not interpret 'more hormones' as 'better luteal support'.

DYDROGESTERONE

- ESHRE: dydrogesterone is probably recommended for LPS (conditional recommendation).
- Evidence quality: moderate (⨁⨁⨁◯).
- ESHRE notes pharmacovigilance reports concerning congenital malformations; causality is not established.
- Use within an evidence-based local protocol and discuss the safety evidence.

Source: ESHRE Guideline on Ovarian Stimulation for IVF/ICSI — 2025 update

WEBINAR

Thank You

Luteal Phase Support

Healthy Luteal Phase → Better Implantation → Brighter Outcomes

Thank you for your time,
interest and participation.

